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THE NUMERIC RELATIONSHIP OF INFECTION TO THE CHEMOTHERAPY OF EXPERIMENTAL TRYPANOSOMIASIS *

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In conducting experiments in the chemotherapy of experimental trypanosomiasis certain factors, as the virulence of the trypanosomes for the test animals and the time when the drug is administered, before or at varying intervals after infection, modify the results with even such a powerful trypanocide as arsenobenzol. As stated in a former communication,¹ the parasitropic effects of a drug or substance under study, and the resistance of the animal to the drug's organotropic effects, are apparently modified, to some extent at least, by an additional factor; namely, whether the animal is infected with small or large numbers of trypanosomes. The object of this paper is to record experiments bearing upon the numeric relationship of infection to the chemotherapy of experimental trypanosomiasis.

METHOD OF STUDY

In our routine chemotherapeutic tests and experiments, a series of rats is infected with a uniform number of *T. equiperdum* 24 hours before the drug is administered intravenously in dosage according to the body weight of each animal. With the number of trypanosomes inoculated by intraperitoneal injection in our tests (100,000 to 150,000 per rat), the parasites are not usually to be found in the peripheral blood until 48 hours after infection, or 24 hours after treatment. In this manner the infection is given a 24-hour start, and is heavy enough to infect the controls in every instance, yet light enough not to mask finer degrees of therapeutic effect on the part of the drug under study.

In the experiments recorded in this communication two strains of *T. equiperdum* were used. Series of rats were infected with increasing numbers of trypanosomes after the method of Kolmer,^{1, 2} each two rats receiving the same number of parasites.

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¹ Kolmer, Jour. Infect. Dis., 1915, 17, p. 79.

² Jour. Infect. Dis., 1915, 16, p. 311.

TABLE 1
ARSENOBENZOL AND *T. EQUIPERDUM* (NEW STRAIN)

Rat	Weight, Gm.	Arsenobenzol Dose per 100 Gm.	Number of <i>T. Equiperdum</i> Injected
1.....	100	.0005	120,000,000
2.....	155	.0005	60,000,000
3.....	135	.0005	36,000,000
4.....	135	.0005	18,000,000
5.....	130	.0005	6,000,000
6.....	100	.0005	3,000,000
7.....	77	.0005	1,200,000
8.....	99	.0005	600,000
9.....	80	.0005	240,000
10.....	75	.0005	60,000
11.....	95	Control	120,000,000
12.....	73	Control	60,000,000
13.....	76	Control	36,000,000
14.....	103	Control	18,000,000
15.....	160	Control	6,000,000
16.....	70	Control	3,000,000
17.....	71	Control	1,200,000
18.....	90	Control	600,000
19.....	83	Control	240,000
20.....	69	Control	60,000

Twenty-four hours later, half the number of infected animals received a constant dose of arsenobenzol according to the body weight of each animal, our object being to determine the influence of a constant dose of arsenobenzol upon rats infected with increasing numbers of the parasites.

The blood of each animal was examined daily for trypanosomes and the results recorded after the scheme given in Table 1.

The results were determined according to whether the animals receiving arsenobenzol remained sterile, or according to the time elapsing before trypanosomes were found in the peripheral blood and the duration of life as controlled by the untreated animals.

In numerous experiments we have found that the sterilizing dose of salvarsan (Ehrlich) and arsenobenzol (Dermatological Research Laboratories) for *T. equiperdum* according to our method, is from 0.001 to 0.002 gm. per 100 gm. of body weight (average 0.0015 gm. per 100 gm.).

Both products in dosage of 0.0005 gm. per 100 gm. of body weight inhibit the multiplication of trypanosomes for a time, but do not usually sterilize the animal.

The results of an experiment with increasing numbers of *T. equiperdum* and 0.0005 gm. arsenobenzol per 100 gm. of rat, are shown in Table 1.

The "new strain" of *T. equiperdum* refers to a fresh strain kindly

TABLE 1—*Continued*
 ARSENOBENZOL AND T. EQUIPERDUM (NEW STRAIN)

Results of Daily Examination of Blood from Tail														
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Few	Few	+	++	++++	++++	++++	D							
Few	+	++	+++	++++	++++	++++	++++	D						
Few	Few	+++	++++	++++	++++	D								
Few	Few	+++	++++	++++	++++	++++	++++	D						
Few	+	+++	++++	++++	++++	++++	++++	++++	D					
Few	+	+++	++++	++++	++++	++++	++++	++++	D					
—	+	++	+++	++++	++++	D								
—	Few	++	+++	++++	++++	D								
—	—	—	—	+	++++	++++	++++	++++	D					
—	—	—	—	—	—	—	—	+	++	+++	++++	++++	D	
Few	Few	+++	++++	++++	D									
Few	+	+++	++++	D										
Few	+	+++	++++	D										
Few	+	++	+++	++++	++++	D								
Few	+	+++	++++	++++	++++	D								
Few	+	+++	++++	D										
Few	+	+++	++++	D										
—	Few	+++	++++	++++	++++	++++	++++	++++	D					
—	Few	+++	++++	++++	++++	D								
—	—	Few	+	+++	++++	++++	D							

KEY TO TABLES

++++ = very large numbers; cannot be counted.
 +++ = large numbers that may be roughly counted.
 ++ = about 10-20 in a field.
 + = about 5-10 in a field.
 Few = 1-2 in a field, or in every other field.
 — = sterile.

sent us by Dr. Wade H. Brown, of Rockefeller Institute. The "old strain" refers to one in use in these laboratories for several years which had a marked virulence and an acquired resistance to the trypanocidal activity of salvarsan and arsenobenzol.

The results of a series of experiments using a constant dose of 0.001 gm. of arsenobenzol per 100 gm. of rat, with increasing numbers of trypanosomes, are shown in Tables 2 to 5.

The results of experiments using 0.002 gm. of arsenobenzol per 100 gm. of rat, with increasing numbers of trypanosomes, are shown in Tables 6 and 7.

SUMMARY OF RESULTS

As shown in the tables the time elapsing before the appearance of trypanosomes in the peripheral blood, or the true incubation, varies according to the number injected. This phase has been reported upon in a former paper.¹ When very large numbers are injected trypanosomes may be found in the peripheral blood within 24 hours after inoculation and are supposed to be in some instances, at least, the adult forms used in inoculation.

As shown in Table 1, the administration of 0.0005 gm. of arseno-

TABLE 2
ARSENOBENZOL AND T. EQUIPERDUM (OLD STRAIN)

Rat	Weight, Gm.	Arsenobenzol Dose per 100 Gm.	Number of T. Equiperdum Injected
1.....	84	.001	1,140,000
2.....	98	.001	912,000
3.....	82	.001	684,000
4.....	132	.001	456,000
5.....	76	.001	228,000
6.....	74	.001	114,000
7.....	93	.001	91,200
8.....	90	.001	68,400
9.....	76	Control	1,140,000
10.....	80	Control	912,000
11.....	68	Control	684,000
12.....	75	Control	456,000
13.....	75	Control	228,000
14.....	70	Control	114,000
15.....	65	Control	91,200
16.....	74	Control	68,400

TABLE 3
ARSENOBENZOL AND T. EQUIPERDUM (OLD STRAIN)

Rat	Weight, Gm.	Arsenobenzol Dose per 100 Gm.	Number of T. Equiperdum Injected
1.....	82	.001	4,840,000
2.....	77	.001	2,884,000
3.....	75	.001	1,936,000
4.....	71	.001	968,000
5.....	103	.001	764,000
6.....	75	.001	580,000
7.....	55	.001	387,200
8.....	55	.001	193,600
9.....	57	.001	96,800
10.....	73	.001	77,440
11.....	50	.001	58,000
12.....	55	.001	38,000
13.....	45	Control	4,840,000
14.....	86	Control	2,884,000
15.....	80	Control	1,936,000
16.....	65	Control	968,000
17.....	60	Control	764,000
18.....	67	Control	580,000
19.....	67	Control	387,200
20.....	53	Control	193,600
21.....	60	Control	96,800
22.....	57	Control	77,440
23.....	81	Control	58,000
24.....	62	Control	38,000

TABLE 2—*Continued*
ARSENOBENZOL AND T. EQUIPERDUM (OLD STRAIN)

Results of Daily Examination of Blood from Tail													
1	2	3	4	5	6	7	8	9	10	11	12	13	14
—	—	—	—	Few	+	++	++++	++++	D	—	—	—	—
—	—	—	—	—	+	++	++++	++++	++++	D	++++	++++	D
D*	—	—	—	—	—	—	—	++	++++	—	—	—	—
—	—	—	—	—	—	—	—	D	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—
Few	+	++	+++	++++	++++	D	—	—	—	—	—	—	—
—	—	Few	+	++++	++++	++++	D	—	—	—	—	—	—
—	—	—	Few	Few	++	++++	D	—	—	—	—	—	—
—	—	+	++	++++	++++	++++	D	—	—	—	—	—	—
D*	—	+	++	++++	++++	++++	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	Few	+	++	++++	++++	D	D	—	—	—
—	—	—	—	—	+	++	+++	+++	++++	—	—	—	—

* Accidental.

TABLE 3—*Continued*
ARSENOBENZOL AND T. EQUIPERDUM (OLD STRAIN)

Results of Daily Examination of Blood from Tail														
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Few	+++	+++	++++	D	—	—	—	—	—	—	—	—	—	—
—	+	++	++++	D	—	—	—	—	—	—	—	—	—	—
—	D*	Few	++	++++	++++	++++	D	—	—	—	—	—	—	—
—	—	+	+++	++	D	++	+++	++++	D	—	—	—	—	—
—	—	—	—	+	+	—	D	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	D	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Few	+++	D	—	—	—	—	—	—	—	—	—	—	—	—
Few	+	++++	++++	D	—	—	—	—	—	—	—	—	—	—
Few	+	++++	++++	++++	++++	D	—	—	—	—	—	—	—	—
—	+	+	++++	++++	++++	+	—	—	—	—	—	—	—	—
—	+	+	++++	++++	+	+	—	—	—	—	—	—	—	—
—	—	Few	++	D	—	—	—	—	—	—	—	—	—	—
—	—	+	++	++++	++++	D	—	—	—	—	—	—	—	—
—	—	D*	+	+	+	+	+	+	+	+	+	+	+	+
—	—	—	+	++	+++	++++	++++	D	—	—	—	—	—	—
—	—	—	Few	+	+	+	+	+	+	+	+	+	+	+
—	—	—	—	Few	+	+	+	+	+	+	+	+	+	+

* Accidental.

TABLE 4
ARSENOBENZOL AND T. EQUIPERDUM (NEW STRAIN)

Rat	Weight, Gm.	Aresenobenzol Dose per 100 Gm.	Number of T. Equiperdum Injected			
				1	2	3
1	122	.001	40,000,000	—	—	—
2	139	.001	24,000,000	—	—	—
3	118	.001	16,000,000	—	—	—
4	117	.001	8,000,000	—	—	—
5	127	.001	4,000,000	—	—	—
6	108	.001	2,400,000	—	—	—
7	127	.001	1,600,000	—	—	—
8	80	.001	800,000	—	—	—
9	110	.001	400,000	—	—	—
10	116	.001	160,000	—	—	—
11	101	.001	80,000	—	—	—
12	138	.001	40,000	—	—	—
13	129	Control	40,000,000	++	++++	++++
14	121	Control	24,000,000	Few	Few	Few
15	90	Control	16,000,000	Few	Few	Few
16	70	Control	8,000,000	++	++++	++++
17	88	Control	4,000,000	Few	++	++
18	120	Control	2,400,000	—	++	++
19	113	Control	1,600,000	—	++	++
20	127	Control	800,000	—	—	++
21	117	Control	400,000	—	—	—
22	87	Control	160,000	—	—	—
23	107	Control	80,000	—	—	—
24	70	Control	40,000	—	—	—

TABLE 5
ARSENOBENZOL AND T. EQUIPERDUM (NEW STRAIN)

Rat	Weight, Gm	Aresenobenzol Dose per 100 Gm.	Number of T. Equiperdum Injected			
				1	2	3
1	141	.001	578,000,000	—	—	—
2	121	.001	192,600,000	—	—	—
3	124	.001	96,300,000	—	—	—
4	137	.001	38,520,000	—	—	—
5	135	.001	19,260,000	—	—	—
6	110	.001	9,630,000	—	—	—
7	153	.001	3,852,000	—	—	—
8	109	.001	1,926,000	—	—	—
9	95	.001	963,000	—	—	—
10	95	.001	385,200	—	—	—
11	116	.001	192,600	—	—	—
12	140	.001	96,300	—	—	—
13	135	Control	578,000,000	++++	D	++
14	100	Control	192,600,000	+	+	++
15	90	Control	96,300,000	++	++++	++++
16	140	Control	38,520,000	++	++++	++++
17	108	Control	19,260,000	—	+	++
18	148	Control	9,630,000	—	+	++
19	132	Control	3,852,000	—	+	++
20	140	Control	1,926,000	+	++++	++++
21	115	Control	963,000	—	+	++
22	96	Control	192,300	—	Few	+
23	80	Control	96,300	—	—	+

TABLE 6
ARSENOBENZOL AND T. EQUIPERDUM (OLD STRAIN)

Rat	Weight, Gm.	Arsenobenzol Dose per 100 Gm.	Number of T. Equiperdum Injected			
				1	2	3
1	95	.002	4,360,000	+	++++	++++
2	160	.002	2,180,000	Few	+	++++
3	110	.002	654,000	—	—	+
4	108	.002	327,000	—	—	+
5	94	.002	218,000	—	—	+
6	85	.002	192,000	—	—	—
7	108	.002	174,000	—	—	—
8	115	.002	130,000	—	—	—
9	87	.002	87,000	—	—	—
10	77	.002	21,000	—	—	—
11	94	.002	13,000	—	—	—
12	110	.002	2,000	—	—	—
13	85	Control	4,360,000	++	++++	D
14	92	Control	2,180,000	++	++++	D
15	80	Control	654,000	Few	+	+++
16	92	Control	327,000	—	Few	+
17	83	Control	218,000	—	Few	+
18	127	Control	192,600	—	—	Few
19	112	Control	174,600	—	—	Few
20	90	Control	130,000	—	—	Few
21	72	Control	87,000	—	—	Few
22	100	Control	21,000	—	—	—
23	95	Control	13,000	—	—	—
24	132	Control	2,000	—	—	—

TABLE 7
ARSENOBENZOL AND T. EQUIPERDUM (NEW STRAIN)

Rat	Weight, Gm.	Aresenobenzol Dose per 100 Gm.	Number of T. Equiperdum Injected			
				1	2	3
1	121	.002	40,000,000	—	—	—
2	118	.002	24,000,000	—	—	—
3	100	.002	16,000,000	—	—	—
4	110	.002	8,000,000	—	—	—
5	124	.002	4,000,000	—	—	—
6	60	.002	2,400,000	—	—	—
7	90	.002	1,600,000	—	—	—
8	135	.002	800,000	—	—	—
9	118	.002	400,000	—	—	—
10	79	.002	160,000	—	—	—
11	73	.002	80,000	—	—	—
12	100	.002	40,000	—	—	—
13	104	Control	40,000,000	Few	++++	++++
14	93	Control	24,000,000	Few	+	++++
15	60	Control	16,000,000	Few	++++	++++
16	98	Control	8,000,000	Few	++++	++++
17	72	Control	4,000,000	Few	+	+
18	69	Control	2,400,000	Few	+	+
19	69	Control	1,600,000	Few	++	++
20	72	Control	800,000	—	+	+
21	70	Control	400,000	—	—	+
22	73	Control	160,000	—	—	—
23	80	Control	80,000	—	—	—
24	68	Control	40,000	—	—	—

TABLE 6—Continued
ARSENOBENZOL AND T. EQUIPERDUM (OLD STRAIN)

Results of Daily Examination of Blood from Tail											
4	5	6	7	8	9	10	11	12	13	14	15
D ++++ ++ ++ +++ — — — — — —	D ++ ++++ ++++ — — — — — —	++++ ++++ ++++ — — — — — —	D D ++++ — — — — — —	++++ — — — — — — — —	++++ — — — — — — — —	++++ — — — D — — —	D Few — — — — — —	+ — — — — — — —	++ — — — — — — —	++++ — — — — — — —	D — — — — — — —
D ++ ++ + ++ Few + — —	+++ ++++ ++++ ++ ++ + Few — —	++++ ++++ ++++ ++++ ++++ ++ ++ ++ —	D ++++ ++++ D ++++ ++++ ++ ++ —	D ++++ ++++ ++++ ++++ ++ ++ — —	D ++++ ++++ ++++ ++++ ++ ++ ++ Few	D D ++++ ++++ ++++ ++++ ++ +	++++ D ++ ++ ++ ++ ++ ++ ++	++++ ++++ ++++ ++++ ++++ ++++ ++++ ++++	D ++++ ++++ ++++ ++++ ++++ ++++ ++++ ++++	D ++++ ++++ ++++ ++++ ++++ ++++ ++++ ++++	D — — — — — — — —

TABLE 7—Continued
ARSENOBENZOL AND T. EQUIPERDUM (NEW STRAIN)

Results of Daily Examination of Blood from Tail											
4	5	6	7	8	9	10	11	12	13	14	15
— — — — — — — — — — — D ++++ ++++ D + ++ ++++ ++++ ++ + — —	— — — — — — — — — — — — ++++ ++++ + ++++ ++++ ++ ++ ++ —	— — — — — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ ++ —	— — — — — — — — — — — — D ++++ ++++ D ++++ ++++ ++++ ++ +	— — — — — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ ++ ++	+ — — — — — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ ++ ++	++ — — — — — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ ++ ++	+++ — — — — — — — — — — — — D — D — D — D — D	++++ + — — — — — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ — —	++++ ++ Few — — — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ — —	D ++++ Few Few Few — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ — —	++++ — Few Few Few — — — — — — — — ++++ ++++ ++++ ++++ ++++ ++++ — —

benzol per 100 gm. of body weight did not influence the trypanosomiasis of those rats infected with 600,000 or more trypanosomes; with smaller numbers of trypanosomes there was a delay or inhibition of development.

In general terms the administration of 0.001 gm. of arsenobenzol per 100 gm. of body weight sterilized rats infected with about 400,000 or less of trypanosomes; when larger numbers of trypanosomes were used in inoculation, sterilization did not result but the appearance of trypanosomes in the peripheral blood was delayed as compared with the controls receiving trypanosomes alone (Tables 2, 3, 4, and 5).

The administration of 0.002 gm. of arsenobenzol per 100 gm. of body weight usually sterilized rats receiving as many as 2,000,000 to 4,000,000 trypanosomes (Table 7). With the resistant strain, which was used in this experiment shortly before being discarded for the purpose of chemotherapeutic researches, the effect of this dose was much less marked (Table 6). As previously stated, this dose of salvarsan or arsenobenzol usually sterilizes animals infected with what may be called a heavy infection, namely, 1,000,000 parasites per rat.

CONCLUSIONS

These experiments demonstrate that in the chemotherapy of trypanosomiasis there is an important relationship between the number of trypanosomes injected into the test animal and the trypanocidal activity on the part of the drug.

This relationship is particularly in evidence with respect to the amount of drug necessary to effect complete sterilization; while rats infected with 500,000 trypanosomes may be sterilized with 0.001 gm. of arsenobenzol per 100 gm. of rat, this is not the case when larger numbers of trypanosomes are injected.

The influence of numbers is less marked when the rats are very heavily infected, as with numbers over 2,000,000. In these instances, arsenobenzol or salvarsan in dose of 0.001 gm. or 0.6 gm. per 60 kilograms of body weight retards the appearance of trypanosomes in the peripheral blood, but does not sterilize. The time of appearance of the parasites in the blood is likewise not greatly influenced by variation in the number used in inoculation.

The numeric relationship of infection to the results of chemotherapeutic experiments is therefore a subject of considerable importance, and more particularly in comparative tests.